REMARKS

The Office Action mailed October 6, 2004 set an initial three (3) month period for response. Accordingly, a timely response without extension of time is presently due January 6, 2005.

Claims 1, 2, 6, 7, 8, 11, and 12 have been amended to more particularly point out and distinctly claim methods of Applicants' invention and correct some minor errors. Withdrawn claims 22 and 26 has also been amended. Applicants submit that these amendments are clearly supported by the specification and claims as filed and give rise to no issue of new matter.

Claims 35 to 40, drawn to non-elected Group III have been cancelled without prejudice to expedite prosecution. Applicants reserve their rights to pursue the subject matter of the cancelled claims in continuing and/or divisional applications as appropriate.

The Election/Restriction Requirement

In a telephonic restriction requirement, the Examiner required restriction to one of the following inventions:

Group I: claims 1 to 21, drawn to a method;

Group II: claims 22 to 34, drawn to a method;

Group III: claims 35 to 40, drawn to devices and kits.

Applicants confirm that in response to the Examiner's telephonic restriction requirement, they provisionally elected the invention of Group I with traverse.

In support of their traverse, Applicants submit that claims 1 to 40, as filed, are sufficiently related to define a coherent invention which is properly examinable as a whole without undue burden on the Examiner.

In particular, Applicants submit that the invention of Group II is properly examinable with the invention of Group I. Both Group I and Group II are directed to methods of quantitation of glycated proteins in a sample. Claims 1 and 6 are directed to quantitation of glycated protein. Claims 4 (ultimately dependent on claim 1) and 10 (ultimately dependent on claim 6) specify that the glycated protein is glycated hemoglobin. Claims 5 (ultimately dependent on claim 1) and 11 (ultimately dependent on claim 6) specify that the glycated protein is glycated albumin.

Claim 12 (also grouped in Group I) is directed to methods of quantitation of glycated hemoglobin.

Applicants note that claim 22, which was grouped with Group II, is directed to methods of quantitation of non-hemoglobin glycated protein in a biological sample. Claims 23 to 34 are dependent or ultimately dependent on claim 22. Applicants submit that these claims are sufficiently related to the methods of Group I, that they may be properly examined together. In particular, Applicants note that the Examiner has examined both claims where the glycated protein is hemoglobin (claims 4, 10 and 12 to 21) and claims where the glycated protein is a non-hemoglobin glycated protein, namely glycated albumin, (claims 5 and 11) in the Office Action mailed October 6, 2004. Applicants submit that the Examiner could expand the scope of examination to cover claims 22 to 34 without undue burden.

In his explanation of his rationale for requiring restriction between Group I and Group II, the Examiner noted:

> In the instant case, the different inventions have different modes of operation because Invention I requires the step of measuring a selected property of a protein, while Invention II requires measuring a property of a labeling agent.

Office Action mailed October 6, 2004, page 2.

Applicants note that claims 12 and 22 both specify making optical readings (see steps (c) and (e) of each claim). Claims 12 specifies that the optical readings are made at a wavelength at which hemoglobin absorbs light. Claim 22 specifies that the optical readings are made at a wavelength at which the non-hemoglobin protein or the protein specific labeling agent absorbs light.

Accordingly, Applicants request that the Examiner reconsider the restriction requirement and reformulate it to include both Groups I and II for purposes of examination.

The Second 112, Second Paragraph Rejections

Claims 1 to 21 stand rejected under 35 U.S.C. §112, second paragraph, as assertedly indefinite.

In particular, the Examiner has pointed out certain informalities regarding antecedent basis and other wording. Although Applicants believe that the claims as filed complied with the second paragraph of Section 112, Applicants note that claims 1, 2, 6, 7, 8, 11, 12, 22 and 26 have

been amended to more particularly point out and distinctly claim the subject matter of provisionally elected Group I and, in the case of claim 22, Group II.

Applicants note that the claims have been amended to clarify antecedent basis for certain of the terms in view of the Examiner's comments. In other situations (for example claims 16 to 17), Applicants submit that there was antecedent basis in the claims as filed for the objected to term.

Applicants note that the Examiner has objected to certain terms as assertedly indefinite. Applicants submit that these objections are not well taken and that, when the terms are considered in the context of what the specification fairly teaches and in view of the level of knowledge and skill in the art, the terms would be clearly understood.

Applicants submit that the claims as presently pending clearly are in compliance with 35 U.S.C. §112, second paragraph.

Applicants request that the Examiner reconsider this rejection and withdraw it.

The Section 102(b) Rejection

Claims 1 to 4 stand rejected under 35 U.S.C. § 102(b) as assertedly anticipated by United States Patent No. 4,269,605 to Dean et al. ("Dean et al.").

This rejection is respectfully traversed; Applicants submit that Dean et al. clearly do not anticipate claims 1 to 4.

Independent claim 1 provides as follows:

> 1. (Currently Amended) A method of quantitation of an amount of a protein which is glycated relative to the total amount of the protein (non-glycated and glycated) in a sample which comprises:
>
> (a) contacting a solid support matrix which comprises a negatively charged group and a hydroxyboryl compound and which has a measurement area, with an aliquot of biological sample sufficient to cover said measurement area;
>
> (b) contacting said solid support matrix with an aliquot of a first buffer wherein said first buffer has a pH selected to allow both glycated and non-glycated forms of the protein to bind to said solid support matrix and wherein said first buffer is applied in an amount sufficient to rinse off protein which does not bind to the solid support matrix;
>
> (c) quantitating amount of the protein bound to said measurement area using measurement of a selected property of said protein to give a first bound protein reading;

(d) contacting said solid support matrix with an aliquot of a second buffer wherein said second buffer has a pH selected to allow the glycated protein to bind to said solid support matrix but where the non-glycated protein does not substantially bind to said solid support matrix wherein said second buffer is applied in an amount sufficient to rinse off the non-glycated protein;

(e) quantitating amount of the protein bound to said measurement area using measurement of the property measured in step (c) to give a second bound protein reading; and

(f) calculating relative amount of glycated protein using said first and second bound protein readings.

Claims 2 to 4 are either dependent or ultimately dependent on claim 1.

Applicants note that in order to anticipate a claim, a single reference must teach every element of that claim. Since Dean et al. clearly do not teach every element of claim 1, Dean et al. cannot anticipate claim 1. Since dependent claims 2 to 4 include further elements in addition to those of claim 1, they also are not anticipated.

Dean et al. appear to describe methods for separating certain glycosylated hemoglobins from non-glycosylated hemoglobins for determining the glycosylated hemoglobin content in lysed blood. In particular, Dean et al. are said to describe methods which comprise:

1. Binding of glycosylated hemoglobin of lysed blood to immobilized or separable dihydroxyboryl reactive agent.
2. Separation of non-glycosylated hemoglobins by washing or removal of resulting complex (e.g., by removing dipstick or by partitioning).
3. Estimation of glycosylated hemoglobin either in situ on or in the reactive agent or after recovery from the reactive agent.

Col. 5, lines 51 to 68.

Applicants note that Dean et al. fail to teach at least two of the steps of Applicants' claim 1, namely steps (b) and (c).

Applicants submit that Dean et al. does not teach step (b) of claim 1, use of a first buffer having a pH where both non-glycated protein and glycated protein are bound to a solid support matrix. In the description of their separation process, Dean et al. teach use of a buffer having a pH at which glycated hemoglobin binds to their support and, optionally, if recovery of the glycosylated hemoglobin is desired, use of a buffer which desorbs the glycosylated hemoglobin

from the support. Dean et al. do not teach use of buffer conditions where both glycosylated and non-glycosylated hemoglobin bind to a support.

Dean et al. also do not describe step (c), making a first bound protein reading. Dean et al. teach making only one measurement of bound protein, glycated hemoglobin. Dean et al. appear to describe measurement of bound glycated hemoglobin by comparison to known standards, if it is not recovered or desorbed before being measured.

Since Dean et al. fail to describe all the elements of claim 1, Dean et al. clearly do not anticipate claim 1.

Claims 2 to 4 are dependent or ultimately dependent on claim 1. Those claims include the elements of claim 1 as well as additional elements. Accordingly, Dean et al. do not anticipate claims 2 to 4 as well.

Applicants request that the Examiner reconsider the present rejection in view of their remarks and withdraw it.

The Section 103 Rejection Over Dean et al. in View of Sanders and May and Richards

Claims 6 to 10 and 12 to 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Dean et al. in view of United States Patent No. 4,407,961 to Sanders ("Sanders") and UK Patent application No. 2 206 411 to May and Richards ("May and Richards").

This rejection is respectfully traversed. Applicants submit that Dean et al. taken in view of Sanders and May and Richards neither suggest nor make obvious the subject matter of claims 6 to 10 and 12 and 21.

Independent claims 6 and 12 provide as follows:

> 6. (Currently Amended) A method for quantitation of an amount of a protein which is glycated relative to the total amount of the protein (non-glycated and glycated) in a biological sample which compromises:
>
> (a) contacting a solid support matrix which comprises a negatively charged group and a hydroxyboryl compound and which has a measurement area with an aliquot of a biological sample sufficient to cover said measurement area;
>
> (b) contacting said solid support matrix with an aliquot of a first buffer, wherein said first buffer has a pH of about 5.0 to about 7.0 and

wherein said first buffer is applied in an amount sufficient to rinse off protein which does not bind to the solid support matrix at a pH of about 5.0 to about 7.0;

(c) quantitating amount of the protein bound to said measurement area using measurement of a selected property of the protein to give a first bound protein reading;

(d) contacting said solid support matrix with an aliquot of second buffer, wherein said second buffer has a pH of about 8.0 to about 10.0 and wherein said second buffer is applied in an amount sufficient to rinse off protein which does not bind to the solid support matrix at a pH of about 8.0 to about 10.0;

(e) quantitating amount of the protein bound to said measurement area using measurement of a selected property of the protein to give a second bound protein reading; and

(f) calculating relative amount of the glycated protein in said sample using said first bound protein reading and said second bound protein reading.

12. A method of quantitation of an amount of hemoglobin which is glycated relative to total amount of hemoglobin (non-glycated and glycated) in a biological sample which comprises;

(a) adding said sample to a sample application site which is in communication with a solid support matrix which comprises a negatively charged group and a dihydroxyboryl compound and which has a measurement area;

(b) adding an aliquot of a first buffer at said sample application site, wherein said first buffer has a pH between about 5.0 and about 7.0;

(c) making a first optical reading of said measurement area at a wavelength at which hemoglobin absorbs light;

(d) adding an aliquot of a second buffer at said sample application site, wherein said second buffer has a pH between about 8.0 and about 10.0;

(e) making a second optical reading of said measurement area at a wavelength at which hemoglobin absorbs light; and

(f) calculating relative amount of glycated hemoglobin in said blood sample using said first and second optical readings.

Claims 7 to 10 are either dependent or ultimately dependent on claim 6. Claims 13 to 21 are either dependent or ultimately dependent on claim 12.

Applicants direct the Examiner's attention to their remarks regarding Dean et al. as set forth hereinabove. As noted above in connection with claim 1, Dean et al. fail to teach or

suggest all of the claimed elements of claims 6 and 12. Applicants note that consideration of the secondary references, Sanders and May and Richards, does not, in view of what Dean et al. would fairly teach or suggest to one of skill in the art, provide the missing elements, or suggest their inclusion so as to make obvious the methods of either claim 6 or 12.

Applicants note that the Examiner appears to admit that Dean et al. did not teach a first buffer in the pH 5.0 to 7.9 range for binding glycated protein to a negatively charged group and a hydroxyboryl compound (see Office Action mailed October 6, 2004, page 9, second paragraph).

Sanders is said to provide an ion-exchange system and method for separating glycosylated hemoglobin from non-glycosylated hemoglobin. Sanders is said to describe an ion-exchange system for selectively binding non-glycosylated hemoglobin in human blood which contains a cation-exchange resin and a zwitterionic buffer having a pH from about 6.4 to 7.2 and a concentration from about 0.02 molar to about 0.1 molar. Sanders expressly teaches that his system selectively binds non-glycosylated hemoglobin, but does not bind glycosylated hemoglobin. (See, Col. 2, lines 32 to 36). Accordingly, Applicants submit that Sanders do not suggest use of a first buffer which allows both glycated and non-glycated protein to their solid support matrix.

May and Richards are said to be directed to assays and methods for determining the proportions of glycated and non-glycated hemoglobin using a device having a first zone which binds only glycated hemoglobin and a second zone which can bind all residual hemoglobin. The first zone is described as comprising immobilized boronic acid and the second zone is described as comprising carrier material adapted to bind non-glycated hemoglobin. Applicants note that May and Richards describe use of only one buffer and with their two-zone support, a first zone which binds only glycated hemoglobin and a second zone which binds non-glycated hemoglobin. The sample is added to the first zone, an aliquot of buffer is added, glycated hemoglobin binds to the first zone and non-glycated hemoglobin is eluted to the second zone where it binds. The two zone assay of May and Richards uses zones with differential binding capabilities and one electing buffer in order to separate glycated hemoglobin from non-glycated hemoglobin.

In view of the substantial differences in the assay methods and formats which Sanders and May and Richards appear to describe, Applicants submit that one of skill in the art would not be likely to combine teachings of Dean at al. with those of Sanders and/or May and Richards in order to suggest or make obvious Applicants' methods. However, as Applicants have noted,

even if such teachings were combined, they would not suggest or make obvious Applicants' methods.

Applicants request that the Examiner reconsider this rejection and withdraw it.

The Section 103(a) Rejection Over Dean et al. in View of Goldstein

Claim 5 stands rejected over 35 U.S.C. § 103(a) as being unpatentable over Dean et al. in view of Goldstein, *Diabetes Care* S18-S20 (1997) ("Goldstein").

Claim 5 is ultimately dependent on claim 1 and specifies that the glycated protein is glycated albumin.

This rejection is respectfully traversed. Applicants submit that Dean et al. considered in view of Goldstein neither suggests nor makes obvious the method of claim 5. As Applicants have noted previously, Dean et al. fail to describe steps (b) and (c) of claim 1.

As noted, Claim 5 specifies that the glycated protein measured is glycated albumin.

As previously noted, Dean et al. fail to teach or suggest Applicant's methods, for determining amounts of glycated protein in relation to total glycated and non-glycated protein.

Goldstein is cited by the Examiner as teaching that detection of glycated albumin may be useful in diabetes. Goldstein appears to review parameters which may be useful to measure in evaluating diabetic patients. One of the parameters mentioned was glycated serum protein, including glycated serum albumin. However, at most Goldstein recognizes that such testing may be useful for certain patients. Goldstein do not teach or suggest appropriate steps to include in such testing in order to supplement Dean et al. Moreover, the combination of Goldstein with Dean et al. does not remedy the deficiencies of what Dean et al. teach or fairly suggest to one of skill in the art which Applicants have previously pointed out.

Applicants request that the Examiner reconsider this rejection and withdraw it.

The Section 103(a) Rejection over Dean et al. in View of Sanders, May and Richards and Goldstein

Claim 11 stands rejected as assertedly unpatentable under 35 U.S.C. §103(a) over Dean et al. in view of Sanders, May and Richards and Goldstein.

This rejection is respectfully traversed. Applicants submit that the cited references, whether considered alone or in combination, neither suggest nor make obvious the method of claim 11.

Claim 11 is ultimately dependent on claim 6 and specifies that the glycated protein determined is glycated albumin.

Applicants direct the Examiner's attention to their remarks regarding the deficiencies of what Dean et al. would teach or suggest to those of skill in the art and how combining the secondary references Sanders and May and Richards would not appropriately supplement Dean et al. or remedy the deficiencies of Dean et al. The further combination of Goldstein with Dean et al. taken in view of Sanders and May and Richards fails to suggest or make obvious the method of claim 11. At most, Goldstein would suggest that measurement of glycated serum protein, including glycated serum albumin, may be useful in evaluating certain diabetic patients, but even in that observation Goldstein is somewhat equivocal.

Accordingly, Applicants submit that Dean et al. taken in view of Sanders, May and Richards and Goldstein, clearly do not suggest or make obvious the method of claim 1.

Applicants request that the Examiner reconsider this rejection and withdraw it.

The Obviousness-type Double Palistry Rejection

The claims 1 to 21 appear to stand previously rejected under the judicially-created doctrine of obviousness-type double palistry over U.S.S.N. 10/062,281.

Applicants note that U.S.S.N. 10/062,281 has become abandoned and is no longer pending.

Applicants submit that this rejection is no longer appropriate and request that it be withdrawn.

CONCLUSION

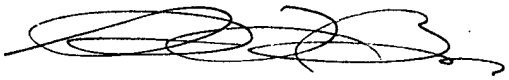
In view of the foregoing, Applicants submit that claims 1 to 21 are allowable. Applicants request that claims 22 to 34 be rejoined for examination and prosecution. Applicants submit that those claims include allowable subject matter. Applicants request that the claims be allowed and passed to issue.

If the Examiner believes that a telephonic interview would expedite prosecution of this Application, he is encouraged to telephone the undersigned Applicant's attorney.

Please charge any fees associated with the submission of this paper to Deposit Account Number 502212. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

PILLSBURY WINTHROP LLP



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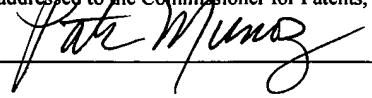

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